## REMARKS

Claims 1, 3-26 and 28-34 are pending after these amendments.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 5, 18, and dependent claim 19 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Claims 5 and 18 have been amended. No new matter is added by these amendments. Support for the amendment to claim 5 can be found, *inter alia*, at page 3, lines 14-19 and at page 10, lines 5-16. Specific support for claim 18 is found at page 5, lines 11-26 and at page 9, lines 1-11. Claim 21 as amended is supported on page 4, lines 30-33.

Rejections Under 35 U.S.C. § 102

**Landegren Does Not Anticipate Claim 1 Since Landegren Does Not Disclose Any Method of Amplifying a Nucleic Acid Template**

The Office rejected claim 1 under 35 U.S.C. § 102(b) as allegedly being anticipated by Landegren et al. (US Patent No. 4,988,617. This rejection is respectfully traversed.

Landegren discloses methods of detecting one or more point mutations in biologically derived DNA or RNA (Col. 2, line 60). But Landegren does not disclose any methods of amplifying a nucleic acid template involving a primer covalently bound to a non-nucleotide carrier molecule, where the non-nucleotide carrier molecule is from a category recited in claim 1 (e.g., a synthetic polymer having nucleophilic functional groups).

The Examiner references the disclosure of 5' aminothymidine and fluorescein as labels of the primers of Landegren (Col. 8, lines 43-62). First, the Examiner refers to fluorescein as containing "nucleophilic functional groups." But claim 1 requires that the member of the Markush group (to which apparent reference is made) is "a synthetic polymer having nucleophilic functional groups." Fluorescein is not a synthetic polymer, as this member of the Markush group requires.

Landegren discloses no method using such a carrier macro-molecule, nor any other member of the Markush group.

Secondly, these components are labels and not carriers, and a person of ordinary skill in the art would not view these components as carrier molecules, but as labels. Claim terms must be interpreted as having the meaning assigned by one of ordinary skill in the art, unless the specification indicates otherwise. *Vivid Technologies, Inc. v. American Science & Eng'g, Inc.*, 200 F.3d 795; 53 USPQ2d 1289 (Fed. Cir. 1999) ("Claims are construed by the court as they would be understood by persons of skill in the field of the invention, for patents are written by and for skilled artisans"); *Loctite Corp. v. Ultraseal Ltd.*, 781 F.2d 861; 228 USPQ 90 (Fed. Cir. 1985) ("Claims should be construed as they would be by those skilled in the art").

And finally, Landegren does not disclose or suggest using a primer covalently bound to a non-nucleotide carrier macromolecule for performing the amplification of a nucleic acid template.

In contrast, claim 1 relates to a process for the amplification of a nucleic acid. As known in the art, amplification is "usually a massive replication especially of a gene or DNA sequence (as in a polymerase chain reaction." (See, http://www.m-w.com/cgi-bin/dictionary?book=Dictionary&va=amplification, attached as Exhibit 1). Because Landegren does not disclose any method of amplifying a nucleic acid template, claim 1 is not anticipated by Landegren. Applicant therefore, respectfully requests reconsideration and withdrawal the rejection.

**Bronstein Does Not Anticipate Claim 18 Because Bronstein Does Not Disclose a First Nucleic Acid Bound to a Non-Nucleotide Carrier Macromolecule And a Second Nucleic Acid Bound to a Non-Nucleotide Carrier Macromolecule**

The Examiner maintained the previous rejection claim 18 under 35 U.S.C. § 102(b) as allegedly being anticipated by Bronstein (U.S. patent No. 5,220,005). This rejection is respectfully traversed.

The Examiner refers to an excerpt at Col. 13, lines 44-61 of Bronstein, disclosing an assay where viral DNA is bound to a nylon or nitrocellulose membrane. The immobilized viral DNA is contacted with a DNA probe specific to the viral DNA and which is labeled with alkaline phosphatase (Bronstein, Col. 13, lines 50-55). The Examiner contends that the membrane that

immobilizes the viral DNA qualifies a "carrier macromolecule" and that Bronstein therefore anticipates claim 18.

The words in claims are to be given their ordinary meaning in the absence of indication in the patent to the contrary. *Rexnord Corp. v. Laitram Corp.* 274 F.3d 1336; 60 USPQ2d 1851 (Fed. Cir. 2001) ("As we have often stated before, as a general rule, all terms in a patent claim are to be given their plain, ordinary meaning as understood by an artisan of ordinary skill"); *Vivid Technologies, infra.*

A person of ordinary skill would not regard a nitrocellulose membrane as a "carrier macromolecule," or even as being a macromolecule at all, as the Examiner contends. Indeed, the use of the term in the specification excludes this strained interpretation. The specification states "In a particularly advantageous aspect of the invention, the carrier macromolecule is itself bound to a solid support" (paragraph 24). And again at paragraph 32, "The invention includes also a nucleic acid bound to a carrier macromolecule, which macromolecule is itself bound to a solid support and the use of such an immobilized nucleic acid as a primer or probe." Therefore, the specification makes it clear that a membrane or solid phase is not a "carrier macromolecule." *Budde v. Harley-Davidson, Inc.*, 250 F.3d 1369; 58 USPQ2d 1801 (Fed. Cir. 2001) ("In construing terms used in patent claims, it is necessary to consider the specification as a whole, and to read all portions of the written description, if possible, in a manner that renders the patent internally consistent."); *Beachcombers, Int'l, Inc. v. WildeWood Creative Products, Inc.*, 31 F.3d 1154; 31 USPQ2d 1653 (Fed. Cir. 1994) ("The correct interpretation of the patent claim in suit is directly supported by the body of the patent, a recognized tool of claim construction").

Bronstein discloses the presence of alkaline phosphatase on <u>one</u> of the nucleic acids in the hybridization, while claim 18 requires that a first nucleic acid is bound to a non-nucleotide carrier macromolecule, and a <u>second</u> nucleic acid is also bound to a non-nucleotide carrier macromolecule. In view of the above explanation, Bronstein does not disclose that a nucleic acid bound to a non-nucleotide carrier macromolecule can be detected by detecting the hybridization between the first and second nucleic acids, which is also required by the claim. Claim 18 requires that <u>both</u> nucleic

acids are bound to a non-nucleotide carrier, which is not disclosed or suggested by Bronstein. Therefore, Bronstein does not anticipate nor render obvious claim 18.

Reconsideration and withdrawal of the rejection is respectfully requested.

Rejections Under 35 U.S.C. § 103

The Examiner has entered several rejections under 35 U.S.C. 103(a) involving combinations of references.

In order to establish a *prima facie* case of obviousness, three criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). MPEP 2142.

**1. Claims 3-4, 7-9, 11, and 13 were rejected under 35 U.S.C. Section 103(a) as allegedly being obvious over Walker *et al.* in view of Gold**

The Office Action dated May 25, 2005 contained an obvious typographical error at page 8, line 2, as the reference to Walker was noted as "US Patent No. 5,4870,723". It is believed that the Examiner intended to reference Walker, US Patent No. 5,470,723. This response has been based on that assumption. If the assumption is incorrect, correction and clarification (and another opportunity to respond) is respectfully requested.

Walker does not describe a method using a primer covalently bound to a carrier molecule for the amplification of a nucleic acid template. The Examiner refers to Figure 1 and Example 1 of Walker. Figure 1 illustrates the process of Strand Displacement Amplification (SDA) disclosed by Walker. Example 1 provides an example of this process. However, neither Figure 1 nor Example 1,

nor any other disclosure in Walker describes the use of a primer bound to a non-nucleotide carrier in the amplification of a nucleic acid sequence.

The Examiner refers to the disclosure regarding alkaline phosphatase of Walker as bound to a primer (Col. 9, line 9). However, this disclosure relates to the use of probe tagged with a label in the detection of a nucleic acid sequence by hybridization, not the amplification of the template. Thus the disclosure referenced by the Examiner fails to disclose the extension of the primer and replication or amplification of a nucleic acid template, and rather discloses its use only in detection by hybridization. Labeled primers are hybridized to amplified sequences and the label identifies the hybridization (and therefore the presence of the sequence).

Walker does not disclose or suggest this technique with reference to any technique for replicating or amplifying nucleic acids. Indeed, it is this type of technique (and its concomitant temperature cycling) that Walker presents his methods as supplanting (Col 3, lines 27-65).

Gold discloses methods for improving the cellular uptake of a nucleic acid ligand. Gold fails to supply the claim limitations missing from Walker, and neither Walker nor Gold provide a motivation for their combination. For these reasons, the cited claims are not rendered obvious by the (improper) combination of Walker in view of Gold.

**2. Claims 10, 12, and 14-17 are rejected under 35 U.S.C. Section 103(a) as allegedly being obvious over Walker *et al.* in view of Gold and further in view of Landegren.**

Walker is discussed above. Gold fails to provide the claim limitations absent in Walker. Gold discloses a method of increasing the cellular uptake of a nucleic acid ligand having an intracellular SELEX target by associating the nucleic acid ligand with a lipophilic compound or a non-immunogenic, high molecular weight compound (Col. 5, lines 30-35). Gold also completely fails to disclose hybridization of a primer covalently bound to a non-nucleotide carrier macromolecule selected from the categories of claim 3 via a divinyl sulfone linkage, and extension of the primer to replicate the template. In addition to the deficiencies of Walker described above, and the failure of Gold to provide missing disclosure, no motivation is provided for combining Walker with Gold. Landegren discloses a method of using a ligase to determine base pairing in the end region of a probe (Col. 2, line 60). The Examiner references the disclosure of Landegren at columns 10-11

with respect to a biotin-labeled primer. But biotin is not a "carrier macromolecule" as that term would be understood by a person of ordinary skill in the art, and biotin also fails to qualify under any of the categories of carrier macromolecules recited in the claims.

Thus, Landegren also fails completely to supply the missing disclosure. Therefore, the present claims are not obvious over Walker in view of Gold.

**3. Additional Rejections Under 35 U.S.C. 103(a)**

The Examiner has put forth several additional rejections of various claims under 35 U.S.C. 103(a), including combinations of

1) Walker in view of Gold, and further in view of Yamane (claim 34);

2) Walker in view of Gold, and further in view of Landegren and Barany (claim 20);

3) Walker in view of Westling (claims 3-6, 8-9, 11, 13, and 23);

4) Walker in view of Westling and further in view of Lihme (claims 24-26, 28, and 30);

5) Walker in view of Westling and Lihme, and further in view of Landegren (claims 29, and 31-33);

6) Gold by itself (claim 21);

7) Gold in view of Urdea (claim 22);

The deficiencies of Walker and Gold have been described above.

None of the other references cited by the Examiner (Landegren, Barany, Yamane, Westling, Lihme, Urdea) nor any (inappropriate) combination of any of these references provides the claim elements missing from Walker and Gold as described above (a requirement explained at MPEP

2142). Furthermore, none of these references provide a motivation for making the proposed combinations. None of the references discloses a method involving the use of a primer bound to a non-nucleotide carrier macromolecule from the groups recited in the claim, hybridization of the primer to a nucleic acid template, and the extension of the primer and replication of the nucleic acid template, as recited in the claims.

Furthermore, the Office rejected claim 21 under 35 U.S.C. § 103(a), as allegedly being unpatentable under Gold *et al*. The Office also rejected claim 22 (which depends on claim 21) under 35 U.S.C. § 103(a), as allegedly being unpatentable under Gold *et al*., and further in view of Urdea (U.S. Patent No. 4,775,619). To expedite prosecution, the solid support in claim 21 has been defined. Because Gold *et al*. fail to teach nucleic acids comprising a non-nucleotide carrier macromolecule that is directly bound to such solid supports, claim 21 as amended is allowable. Thus, Applicants respectfully request that these rejections be withdrawn.

Reconsideration and withdrawal of these rejections is respectfully requested.

**Impermissible Hindsight**

It is noted that case law clearly establishes that it is error to reconstruct the claimed invention from the prior art by using the claim as a "blueprint." When prior art references require selective combination to render obvious a subsequent invention, there must be some reason for the combination other than the hindsight obtained from the invention itself. *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132; 227 USPQ 543 (Fed. Cir. 1985). Case law also makes clear that the best defense against hindsight-based obviousness analysis is the rigorous application of the requirement for a showing of a teaching or motivation to combine the prior art references. *Ecolochem, Inc., v. Southern California Edison Co*., 227 F.3d 1361; 56 USPQ2d 1065 (Fed. Cir. 2000).

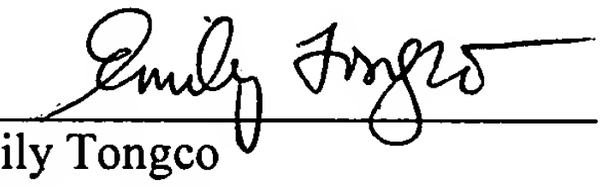
## CONCLUSION

In view of the above, the pending claims are believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims, and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 577212000101. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: September 21, 2005

Respectfully submitted,

By 

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# Merriam-Webster Online Dictionary

Thesaurus

2 entries found for **amplification**.
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Main Entry: **am·pli·fi·ca·tion**
Pronunciation: "am-pl&-f&-'kA-sh&n
Function: *noun*
**1 a :** an act, example, or product of amplifying **b :** a usually massive replication especially of a gene or DNA sequence (as in a polymerase chain reaction)
**2 a :** the particulars by which a statement is expanded **b :** an expanded statement

**EXHIBIT 1**